

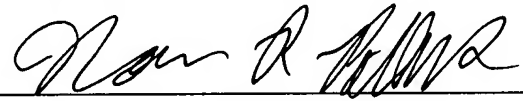
**REMARKS**

Applicant respectfully requests that the above amendments be entered for purposes of the present application. Claims 1-8 are pending and claims 1-6 have been amended herein. It is submitted that no new matter has been added.

This Preliminary Amendment is believed to be timely filed. If a petition for extension of time and/or any other fees are required, the U.S. Patent and Trademark Office is specifically authorized to charge such fee to Deposit Account No. 23-2820 in the name of Wolf, Block, Schorr & Solis-Cohen LLP. An early and favorable action on the merits is respectfully requested.

Respectfully submitted,

Wolf, Block, SCHORR & SOLIS-COHEN LLP

By:   
Noam R. Pollack  
Reg. No. 56,829

Wolf, Block, Schorr & Solis-Cohen LLP  
250 Park Avenue  
New York, New York 10177  
(212) 883-4922  
(212) 672-1122 fax

1  
 New polymorphic forms of ondansetron, processes for  
 preparing them, pharmaceutical compositions containing  
 them and their use as antiemetics

5 **Field of the invention**

This invention relates to a new polymorphs of  
 (±)1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-  
 yl)methyl]-4H-carbazol-4-one, known under the INN of  
 ondansetron.

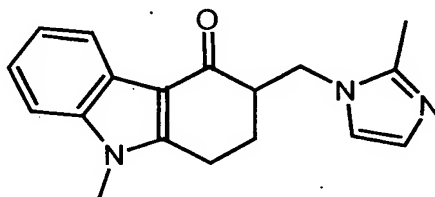
10

This invention also relates to a processes for  
 preparing said polymorphs, to pharmaceutical compositions  
 containing ~~them-it~~ and to ~~their-its~~ use in the treatment  
 and prophylaxis of nausea and vomiting.

15

**Background of the invention**

The compound (±)1,2,3,9-tetrahydro-9-methyl-3-[(2-  
 methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is known  
 under the INN of ondansetron and has the following  
 20 structure:



Ondansetron is a selective antagonist of the 5-  
 HT<sub>3</sub> receptor, which is marketed as an antiemetic.

25

Patent GB 2153821 describes ondansetron, its salts  
 and solvates. In particular, the preparation of base  
 ondansetron is described in several examples. Thus, in  
 example 4, the preparation of base ondansetron is  
 30 described by methylation with dimethyl sulphate in  
 dimethylformamide; the product obtained melts with

2

decomposition at 223°C - 224°C. In example 7, base  
ondansetron is obtained by treatment of 3-  
[(dimethylamine)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-  
carbazol-4-one hydrochloride with 2-methylimidazol in  
5 water, to yield ondansetron with a melting point of 221°C  
- 221.5°C, which following recrystallisation in methanol  
gives a melting point of 231°-232 °C. In example 8, the  
preparation of base ondansetron is described by treatment  
of 1,2,3,9-tetrahydro-9-methyl-3-methylene-4H-carbazol-4-  
10 one with 2-methylimidazol in water followed by  
recrystallisation in methanol, to yield ondansetron with a  
melting point of 232°-234 °C with decomposition. In  
example 18, the preparation of base ondansetron is  
described by reaction of 3-(chloromethyl)-1,2,3,9-  
15 tetrahydro-9-methyl-4H-carbazol-4-one with 2-methyl-  
imidazol in DMF (dimethylformamide), which following  
purification by column chromatography yields ondansetron  
with a melting point of 228°-229°C. In example 19 the  
preparation of base ondansetron is described by oxidation  
20 of 2,3,4,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-  
yl)methyl]-1H-carbazol maleate with 2,3-dichloro-5,6-  
dicyano-1,4-benzoquinone in THF (tetrahydrofuran), which  
following purification by column chromatography yields  
ondansetron with a melting point of 227°C-228.5°C. Example  
25 20 describes the preparation of base ondansetron by  
oxidation of 2,3,4,9-tetrahydro-9-methyl-3-[(2-methyl-1H-  
imidazol-1-yl)methyl]-1H-carbazol-4-ol with 2,3-dichloro-  
5,6-dicyano-1,4-benzoquinone in THF, which following  
purification by column chromatography yields ondansetron  
30 with a melting point of 227.5-229°C.

Patents GB 2220352, EP 385517 and EP 276559 also  
describe the preparation of ondansetron in accordance with  
example 7 of the above-cited patent, giving a melting  
35 point that coincides with that mentioned in said example.

Other processes have also been described for preparing ondansetron, which processes yield ondansetron with the following melting points: in patent EP 221629, 5 following purification by column chromatography, it decomposes at 215-216°C; in patent EP 219929, following purification by column chromatography, it melts at 216-218°C and, following recrystallisation in methanol, at 227.5-228.5°C; and, finally, in patent ES 2043535, 10 following recrystallisation in methanol, it melts at 227-228.5°C.

That is, all the references mentioned above describe ondansetron with very variable melting points 15 that range from 215°C to 234°C. Following purification by column chromatography they remain variable, from 215°C to 229°C, and following recrystallisation in methanol the melting points rise and centre around 230°C (227-234°C).

20 International patent WO 03093260 discloses two crystalline forms of base ondansetron, one with a melting point similar to that described in the preceding references and another with a higher melting point, denominated, respectively, Form A and Form B. Form B has a 25 melting point of  $244 \pm 2^\circ\text{C}$  and a powder X-ray diffraction pattern that is characterised by the following peaks: 11.0; 11.2; 14.9; 15.5; 15.9; 16.5; 20.6; 21.4; 23.1; 23.5; 24.2; 24.7; 24.8; 25.8; 26.9; 28.1 °2 $\theta$ . Its preparation is described by dissolving base ondansetron in 30 ethanol or methanol at reflux temperature and subsequent cooling. Form A is characterised by a powder X-ray diffraction pattern that presents the following peaks: 11.0; 11.2; 14.8; 15.4; 16.4; 20.6; 21.4; 23.2; 24.1; 24.7; 25.4; 25.9; 26.7; 27.8 °2 $\theta$ . The preparation of Form 35 A is described by recrystallisation of ondansetron in N,N-

dimethylformamide and by recrystallisation in 1-butanol.

The examples described disclose the preparation of 5 polymorphic forms of ondansetron solely at a scale of a few grams or a maximum of 1.1 kg. Furthermore, in spite of the small amounts of product obtained, the volume of solvent that has to be used is very high (60 L of solvent are required to prepare the maximum amount described, i.e. 10 1.1 kg), thereby hindering its large-scale production.

It is therefore recommendable to have new stable polymorphic forms of ondansetron and processes for manufacturing them that permit the product to be produced 15 at industrial scale.

#### Description of the invention

The subject-matter of the present invention is to provide ~~three~~one different polymorphic forms of 20  $(\pm)$ 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, known under the INN of ondansetron.

Thus, a first aspect of the invention relates to a 25 new polymorphic form of ondansetron called, hereinafter, ~~Form C, which is characterised by presenting a powder X-ray diffraction pattern, using  $K\alpha_1$  radiation of Cu, in accordance with Figure 1.~~

30 ~~———— A second aspect of the invention relates to a new polymorphic form of ondansetron called, hereinafter, Form D, which is characterised by presenting a powder X-ray diffraction pattern, using  $K\alpha_1$  radiation of Cu, in accordance with Figure 2.~~

~~A third aspect of the invention relates to a new polymorphic form of ondansetron called, hereinafter, Form E, which is characterised by presenting a powder X-ray diffraction pattern, using  $K\alpha_1$  radiation of Cu, in accordance with Figure 3~~1~~.~~

Also subject-matter of the present invention ~~are~~ is a processes for preparing the new polymorphic forms of ondansetron denominated Forms ~~C, D and E~~.

10

Another aspect of the present invention is a pharmaceutical composition that contains ~~any of the said~~ new polymorphic forms of ondansetron, denominated Forms ~~C, D and E~~.

15

Yet another aspect of the invention is the use of the new polymorphic forms of ondansetron denominated Forms ~~C, D and E~~ for manufacturing a drug for the treatment and prophylaxis of nausea and vomiting.

20

And an additional aspect of the invention is a therapeutic method for the treatment and prophylaxis of post-operative nausea and vomiting and for the control of nausea and vomiting induced by radiotherapy and cytotoxic chemotherapy.

#### Description of the figures

~~Figure 1 shows the powder X-ray diffraction pattern of the Form C. The y axis represents the intensity (in counts) and the x-axis represents the angle 2-Theta.~~

30

~~Figure 2 shows the powder X-ray diffraction pattern of the Form D.~~

Figure 3-1 shows the powder X-ray diffraction pattern of the Form E.

~~Figure 4 shows the low-frequency Raman spectrum of Forms C, D and E. The y-axis shows the Raman intensity (in A.U., arbitrary units) and the x-axis the frequency.~~

## 5 Detailed description of the invention

The ~~three~~ polymorphic forms of ondansetron, subject-matter of the present invention, ~~are~~ is identifiable by ~~their~~ its powder X-ray diffraction patterns:

10

~~Form C, to which the first aspect of the invention relates, is characterised by a powder X-ray diffraction pattern that presents two characteristic peaks at 14.97 and 20.86° 2 $\theta$  and presents no peaks beneath 6.5° 2 $\theta$ . To a~~  
15 ~~lesser extent, the phase is also characterised by the peak of 25.50° 2 $\theta$ . The diffraction pattern of Form C presents, in relation with that of the other two polymorphs also subject-matter of this invention, a lower number of peaks in the angle interval 5 — 30° 2 $\theta$ . Table 1 shows the peaks~~  
20 ~~observed in a powder X-ray diffraction pattern of Form C using the conditions for providing the diffraction pattern described below. Said Table 1, further includes the relative intensity values of said peaks as additional information.~~

25

Table 1

$2\theta$ ( $^{\circ}$ )	$I/I_0$
7.18	96
10.96	100
13.13	34
<b>14.97</b>	36
16.08	39
16.42	34
19.73	19
<b>20.86</b>	41
21.82	20
24.08	70
24.70	47
25.50	52
26.73	30
27.59	20
28.97	22

5            ~~Form C presents a powder X-ray diffraction pattern, using the  $K\alpha_1$  radiation of Cu, in accordance with Figure 1.~~

10            ~~Form D, to which the second aspect of the invention relates, is characterised by a powder X-ray diffraction pattern that presents peaks at 11.29°, 14.58°, 17.16°, 18.89°, 20.28°, 21.22°, 25.06° and 27.49° — 20.~~  
 Table 2 shows the peaks observed in a powder X-ray diffraction pattern of Form D. Said Table 2 further  
 15 includes the relative intensity values of said peaks as additional information.

Table 2

$2\theta(^{\circ})$	$I/I_0$
5.58	16
7.10	99
7.26	49
10.77	58
10.92	86
<b>11.29</b>	60
13.23	50
13.65	15
<b>14.58</b>	43
14.74	24
15.23	21
15.38	23
15.92	30
16.22	37
16.48	42
<b>17.16</b>	18
17.86	15
<b>18.89</b>	18
<b>20.28</b>	39
20.71	32
<b>21.22</b>	40
21.98	24
22.84	16
23.53	17
24.12	74
24.75	68
<b>25.06</b>	100
26.03	40
26.17	39
26.56	31
26.79	24
<b>27.49</b>	25
27.91	21
28.75	20
29.41	18

Form D presents a powder X ray diffraction pattern, using the  $K\alpha_1$  radiation of Cu, in accordance with 5 Figure 2.

Form E, to which the third first aspect of the

invention relates, is characterised by a powder X-ray diffraction that presents peaks at 6.29°; 11.09°; 11.88°; 12.69°; 14.97° (~~this last peak being also present in the diffraction pattern of Form C~~) and a doublet 5 (24.96°; 25.17°) 20. Table 3—1 below shows the peaks observed in a powder X-ray diffraction pattern of Form E. Table 3—1 further shows, as additional information, the relative intensity of said peaks.

10

Table 31

2 $\theta$ (°)	I/I <sub>0</sub>
<b>6.29</b>	17
7.06	67
10.50	16
<b>11.09</b>	100
<b>11.88</b>	13
<b>12.69</b>	16
13.10	32
13.57	16
<b>14.97</b>	48
16.33	53
16.93	17
17.40	15
18.58	13
19.28	19
20.71	38
21.08	23
21.28	30
22.10	20
24.12	48
24.71	41
<b>24.96</b>	60
<b>25.17</b>	87
25.73	24
26.65	34
26.93	21
28.18	19
28.53	17
29.34	15
29.76	15

Form E presents a powder X-ray diffraction

pattern, using the  $K\alpha_1$  radiation of Cu, in accordance with Figure 31.

Advantageously, Form E can also be prepared in a manner reproducible at industrial scale, which makes it the optimum crystalline form of ondansetron for marketing and, therefore, the preferred form.

The powder X-ray diffraction patterns were obtained with  $K\alpha_1$  radiation of Cu, using an INEL CPS-120 appliance with Ge primary monochromator and in transmission geometry with the samples inside 0.5 mm diameter Lindemann glass capillary tubes. The error in determination of the position of the peaks can be estimated at  $\pm 0.05^\circ 2\theta$ .

~~Differences were also discerned between the three polymorphic forms C, D and E in the low-frequency region (between 15 and 150  $\text{cm}^{-1}$ ) of the Raman spectra, as shown in Figure 4. The Raman spectra of Forms C and D are more similar to each other, while they show a clear spectral difference in relation to Form E. The Raman technique is therefore not very suitable for distinguishing Forms C and D from one other, although it does permit these two forms to be distinguished from Form E.~~

~~The Raman spectra were obtained using Jobin-Yvon T64000 equipment with an argon laser, and the determination was carried out using an excitation wave of 514.5 nm and laser power between 30 and 35 mW.~~

The ~~three~~ polymorphic forms of the present invention presents a melting points in a range of 240-247  $^\circ\text{C}$ . The melting points was ~~ere~~ determined by DSC, on the basis of the melting peak, using an aluminium crucible

with perforated lid at a heating rate of 10 °C/min. Taking into account that the melting temperatures of the three polymorphs of the invention are similar, and given that base ondansetron melts with decomposition to release 5 2-methylimidazol, melting temperature is not considered to be a characteristic that permits the three forms of the invention to be distinguished from one another.

There follows a detailed description of the 10 processes for preparing the three polymorphs denominated Forms C, D and E of the invention.

Thus, Form C can be obtained by addition of a precipitating solvent to a saturated solution of base 15 ondansetron at room temperature. More specifically, Form C can be prepared by means of a process that comprises:

- a) preparation of a saturated solution of base ondansetron at room temperature in dichloromethane;
- b) precipitation of the crystalline form by addition of a 20 C<sub>5</sub>-C<sub>7</sub> alkane; and
- c) recovery of the crystalline form.

Preferably, said C<sub>5</sub>-C<sub>7</sub> alkane is chosen from n-hexane or n-pentane.

25

Form D can be prepared by a process that comprises:

- a) dissolution of base ondansetron in a C<sub>1</sub>-C<sub>4</sub> alcohol at reflux;
- 30 b) addition of t-butyl methyl ether followed by cooling; and
- c) recovery of the crystalline form.

Preferably, said C<sub>1</sub>-C<sub>4</sub> alcohol is methanol.

35

This invention ~~also~~ provides a process for manufacturing Form E. Said process comprises:

- a) dissolution of the ondansetron hydrochloride in a mixture of a C<sub>1</sub>-C<sub>3</sub> alcohol and water;
- 5 b) precipitation of the base ondansetron by basification of the solution;
- c) filtering the solid and washing with water;
- d) suspension of the water-moistened solid obtained in stage c) with methanol at reflux with stirring; and
- 10 e) recovery of the crystalline form;
- f) and drying the product thus obtained.

Preferably, said C<sub>1</sub>-C<sub>3</sub> alcohol is methanol.

15       The basification of stage b) can be carried out by means of addition of a solution of sodium hydroxide, potassium hydroxide or aqueous ammonia. Preferably, the basification of stage b) is carried out by addition of an aqueous ammonia solution. Advantageously, the basification  
20 with aqueous ammonia produces ammonium chloride as a residue, which is much more soluble in water and in alcohols than sodium or potassium chloride and therefore much easier to eliminate.

25       Advantageously, said process permits Form E to be obtained in a manner perfectly reproducible at industrial scale. Moreover, as it does not require complete dissolution of the base ondansetron in an alcohol, a solvent in which it is not very soluble, it permits  
30 greater amounts of product to be obtained with very much lower volumes of solvent in comparison with the prior art.

Form E can also be prepared at laboratory scale by means of a process that comprises:

- a) dissolution of the base ondansetron in a C<sub>1</sub>-C<sub>4</sub> alcohol at reflux;
- b) addition of ethyl acetate followed cooling and concentration by slow evaporation at room temperature
- 5 and
- c) recovery of the crystalline form.

Preferably, said C<sub>1</sub>-C<sub>4</sub> alcohol is methanol.

10 Recovery of ~~any of the~~ polymorphic forms of the present invention is carried out by filtering the solid and drying, using conventional methods.

In this invention, "a C<sub>1</sub>-C<sub>4</sub> alcohol" is taken to  
15 mean methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol.

~~In this invention, "a C<sub>5</sub>-C<sub>7</sub> alkane" is taken to mean n-pentane, n-hexane, n-heptane.~~

20

The base ondansetron and the ondansetron hydrochloride used as starting product to prepare the polymorphic forms of the present invention can be prepared by any of the processes described in the literature.

25 Preferably, they are obtained in accordance with the general process described in patent ES 2043535, whose industrial application is carried out with hydrochloric acid as acid catalyst, in a mixture of isopropyl alcohol and water as solvent, which permits the ondansetron to be

30 isolated directly in the form of hydrochloride. The base ondansetron can in turn be obtained by basifying a solution of said hydrochloride.

Also subject-matter of the present invention is a  
35 pharmaceutical composition that contains ~~any of the~~ said

new polymorphic forms of ondansetron denominated  
Forms ~~C, D or~~ E in a therapeutically active amount and with  
a suitable amount of at least one excipient.

5           The compositions provided by the present invention  
can be administered by any suitable route, but preferably  
orally or parenterally.

          The compositions for parenteral or topical  
10 administration can be presented in the form of injectable  
solutions, intravenous solutions, infusions, suppositories  
or transdermal systems. The pharmaceutical compositions  
for oral administration can be solids such as tablets or  
capsules prepared by the conventional means with  
15 pharmaceutically acceptable excipients, or liquids such as  
aqueous or oleous solutions, syrups, elixirs, emulsions or  
suspensions prepared by the conventional means with  
pharmaceutically acceptable additives.

20           Tablets and injectable or intravenous solutions  
are preferred forms of oral and parental administration,  
respectively.

          An especially preferred pharmaceutical form for  
25 administration of Forms ~~C, D and~~ E of ondansetron are is  
orally disintegrating tablets (also called  
buccodispersable). Buccodispersable tablets are taken to  
mean uncoated tablets for placing in the mouth and having  
the advantage that they disintegrate rapidly before being  
30 swallowed. Various types of technologies have been  
described for making tablets of this type, and they are  
known to experts in the subject. Especially preferred are  
those disclosed in international patent application WO  
03103629.

Said pharmaceutical forms can contain a dose of  
any of the Forms C, D and E, preferably a dose of 2-10 mg.

In accordance with conventional pharmaceutical  
5 practice, the excipients for the tablet forms can include  
diluents, disintegrants, wetting agents, lubricants,  
colorants, flavourings or other conventional adjuvants.  
Thus, typical tablet excipients include, for example,  
lactose, microcrystalline cellulose, corn starch,  
10 hypromellose, magnesium stearate, macrogol,  
polyvinylpyrrolidone, manitol.

The injectable formulations in accordance with the  
invention include, preferably, aqueous solutions, with  
15 conventional excipients for injectable formulations  
including sodium citrate, citric acid, sodium chloride,  
together with water for injections.

Also subject-matter of the invention is the use of  
20 any of Forms C, D and E for manufacturing a drug for the  
treatment and prophylaxis of post-operative nausea and  
vomiting and for the control of nausea and vomiting  
induced by radiotherapy and cytotoxic chemotherapy.

25 Also subject-matter of the present invention is a  
therapeutic method for the treatment and prophylaxis of  
post-operative nausea and vomiting and for the control of  
nausea and vomiting induced by radiotherapy and cytotoxic  
chemotherapy, which consists in administering to a patient  
30 who so requires a therapeutically effective amount of any  
of the Forms C, D or E, preferably in a dose of between 2-  
10 mg.

**Experimental Part**

There follow by way of non-restrictive illustration of the invention the following examples.

**EXAMPLES OF SYNTHESIS****5 ~~Example 1~~****~~Preparation of Base ondansetron Form C~~**

~~492 mg of base ondansetron are dissolved in 35 mL of dichloromethane. 18 mL of n-hexane are added and crystals~~  
10 ~~are seen to precipitate. The resulting suspension is stirred for 10 minutes and filtered. The white solid obtained is dried at 40°C to constant weight. 137 mg of base ondansetron Form C (28%) is obtained.~~

**15 ~~Example 2~~****~~Preparation of Base ondansetron Form C~~**

~~146 mL of n-pentane is added to a stirred solution of 4 g of base ondansetron in 284 mL of dichloromethane at 20-~~  
20 ~~22°C, and crystals are seen to precipitate. The resulting solution is stirred for 10 minutes and filtered. The white solid obtained is dried at 40°C to constant weight. 2 g of base ondansetron Form C (50%) is obtained.~~

25

**~~Example 3~~****~~Preparation of Base ondansetron Form D~~**

30 ~~A stirred solution of 4 g of base ondansetron in 178 mL of methanol is heated at reflux to total dissolution. 509 mL of t-butyl methyl ether is added slowly and the heating then switched off and the mixture left to cool slowly with stirring down to 20-22 °C. The resulting suspension is~~

~~filtered and the white solid obtained is dried at 40°C to constant weight. 2.4 g of base ondansetron Form D (60%) is obtained.~~

#### 5 **Example 41**

##### **Preparation of Base ondansetron Form E (laboratory method)**

A stirred solution of 4 g of base ondansetron in 200 mL of methanol is heated at reflux to total dissolution. 480 mL  
10 of ethyl acetate is added slowly and the heating then switched off and the mixture left to cool slowly down to 20-22 °C. The stirring is stopped and the mixture is left to concentrate slowly with the flask open for 20-30 days until crystals appear, which are filtered and dried at  
15 40°C. 1 g of ondansetron Form E (25%) is obtained.

#### **Example 52**

##### **Preparation of Base ondansetron Form E (industrial plant 20 method)**

A stirred suspension of 16 kg of ondansetron hydrochloride in 80 L of methanol and 80 L of water is heated at 30 °C to total dissolution. 6 L of 25% aqueous ammonia is added over the course of 2 hours, until pH 9 is reached. Base  
25 ondansetron precipitates out and the resulting suspension is heated to 35 °C and stirred at that temperature for 1 hour. It is then cooled to 22-25 °C and the suspension is centrifuged. The resulting cake is washed with water (2 x 40 L) and suspended again in 60 L of water. The suspension  
30 is stirred at 35 °C for 30 minutes, cooled to 22-25°C and centrifuged again, washing finally with water (2 x 40 L). The water-moistened solid is suspended in 180 L of methanol and the mixture brought to reflux with stirring for 1 hour. The suspension fluidises but does not reach  
35 dissolution. It is cooled to 20-22 °C and the suspension

is stirred for 30 minutes. It is cooled to 0-5 °C and the suspension is stirred for 1 hour at that temperature. The suspension is centrifuged and the cake washed with 20 L of cold methanol. The product is dried at 60°C in vacuo for 15 hours. 10.8 kg of base Ondansetron Form E (84%) is obtained.

- . -

## CLAIMS

~~1. Polymorphic Form C of base ondansetron,  
5 characterised in that its powder X-ray diffraction pattern  
presents characteristic peaks at 14.97 and 20.86° 2θ and  
presents no peaks beneath 6.5° 2θ.~~

~~2. Polymorphic Form D of base ondansetron,  
10 characterised in that its powder X-ray diffraction pattern  
presents characteristic peaks at 11.29°, 14.58°, 17.16°,  
18.89°, 20.28°, 21.22°, 25.06° and 27.49° 2θ.~~

~~3. Polymorphic Form E of base ondansetron,  
15 characterised in that its powder X-ray diffraction pattern  
presents characteristic peaks at 6.29°, 11.09°, 11.88°;  
12.69°, 14.97° and a doublet at (24.96°, 25.17°) 2θ.~~

~~4. Polymorphic form according to Claim 1,  
20 characterised in that its powder X-ray diffraction pattern  
also presents a peak at 25.50° 2θ.~~

~~5. Polymorphic form according to Claim 4,  
characterised in that its powder X-ray diffraction pattern  
25 presents the following peaks:~~

<del>2θ (°)</del>
<del>7.18</del>
<del>10.96</del>
<del>13.13</del>
<del>14.97</del>
<del>16.08</del>
<del>16.42</del>
<del>19.73</del>
<del>20.86</del>

20

21.82
24.08
24.70
25.50
26.73
27.59
28.97

~~6. Polymorphic form according to Claim 5, characterised in that it presents a powder X-ray diffraction pattern in accordance with Figure 1.~~

5

~~7. Polymorphic form according to Claim 2, characterised in that its powder X-ray diffraction pattern presents the following peaks:~~

2 $\theta$ (°)
5.58
7.10
7.26
10.77
10.92
11.29
13.23
13.65
14.58
14.74
15.23
15.38
15.92
16.22
16.48
17.16
17.86
18.89
20.28
20.71
21.22
21.98
22.84

21

23.53
24.12
24.75
25.06
26.03
26.17
26.56
26.79
27.49
27.91
28.75
29.41

~~8. Polymorphic form according to Claim 7, characterised in that presents a powder X-ray diffraction pattern in accordance with Figure 2.~~

5

92. Polymorphic form according to Claim 31, characterised in that its powder X-ray diffraction pattern presents the following peaks:

2 $\theta$ (°)
6.29
7.06
10.50
11.09
11.88
12.69
13.10
13.57
14.97
16.33
16.93
17.40
18.58
19.28
20.71
21.08
21.28
22.10
24.12
24.71

24.96
25.17
25.73
26.65
26.93
28.18
28.53
29.34
29.76

~~103.~~ Polymorphic form according to Claim 92, characterised in that it presents a powder X-ray diffraction pattern in accordance with Figure 31.

5

~~11. Process for preparing the polymorphic form according to Claim 1, characterised in that it comprises:~~

- ~~a) preparation of a saturated solution of base ondansetron at room temperature in dichloromethane;~~
- 10 ~~b) precipitation of the crystalline form by addition of a C<sub>5</sub>-C<sub>7</sub> alkane; and~~
- ~~c) recovery of the crystalline form.~~

~~12. Process according to Claim 11, characterised in that said C<sub>5</sub>-C<sub>7</sub> alkane is n-hexane or n-pentane.~~

15

~~13. Process for preparing the polymorphic form according to Claim 2, characterised in that comprises:~~

- ~~a) dissolution of base ondansetron in a C<sub>1</sub>-C<sub>4</sub> alcohol at~~
- 20 ~~reflux;~~
- ~~b) addition of t-butyl-methyl-ether followed by cooling;~~
- ~~and~~
- ~~c) recovery of the crystalline form.~~

25 ~~144.~~ Process for preparing the polymorphic form according to Claim 31, characterised in that it comprises:

- a) dissolution of the ondansetron hydrochloride in a mixture of a C<sub>1</sub>-C<sub>3</sub> alcohol and water;

- b) precipitation of the base ondansetron by basification of the solution;  
c) filtering the solid and washing with water;  
d) suspension of the water-moistened solid obtained in  
5 stage c) with methanol at reflux with stirring; and  
e) recovery of the crystalline form;  
f) and drying the product thus obtained.

~~155.~~ Process according to ~~any of claims 13 or 14~~  
10 4, characterised in that said alcohol is methanol.

~~166.~~ Process according to Claim ~~144~~, characterised  
in that the basification of stage b) is carried out by  
addition of an aqueous ammonia solution.

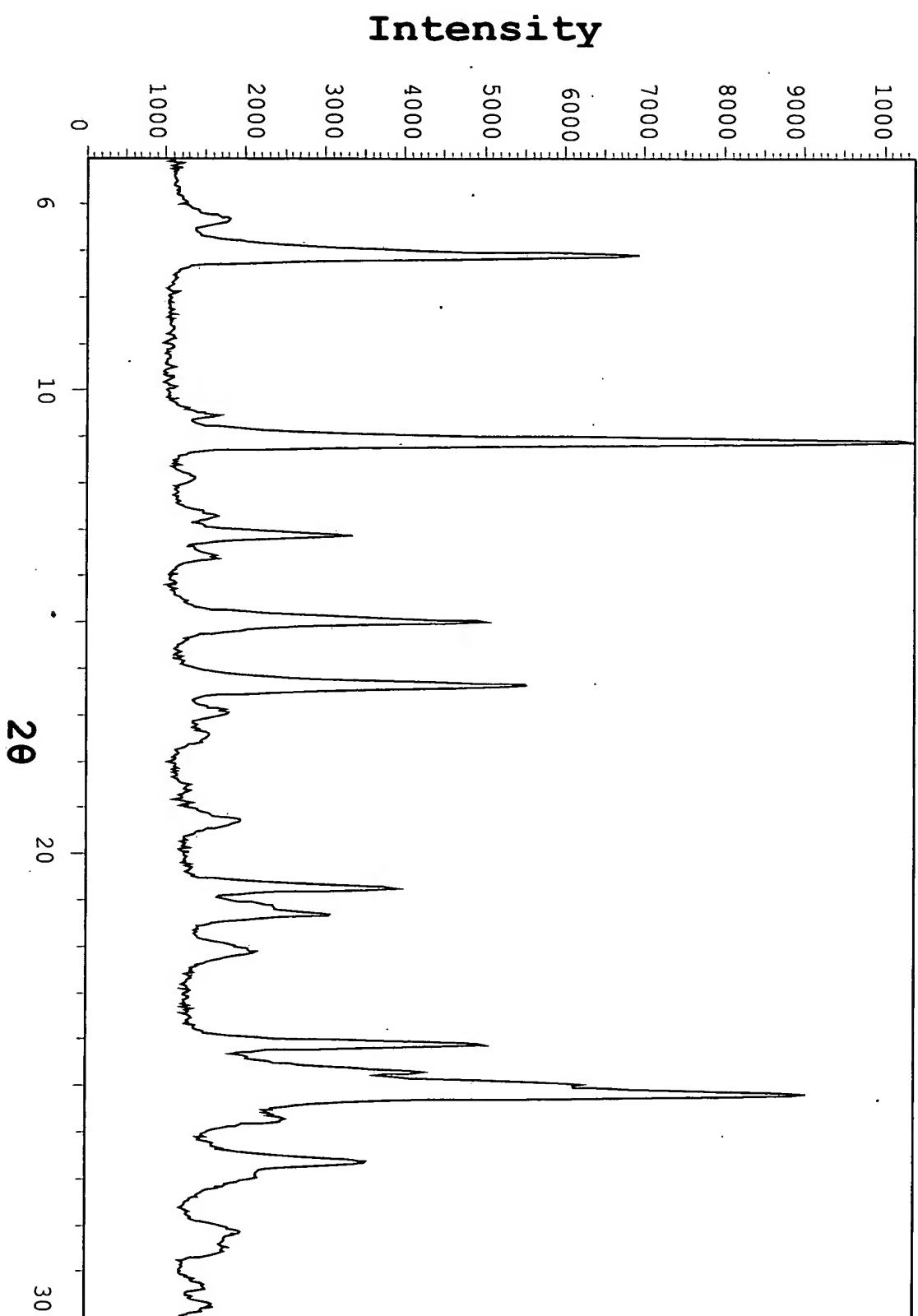
15 ~~177.~~ Pharmaceutical composition that includes a  
polymorphic form according to ~~any of claims 1 to 10~~ 1, in a  
therapeutically active amount and with a suitable amount of  
at least one excipient.

20 ~~188.~~ A Polymorphic form according to ~~any of~~  
claims ~~1 to 10~~ for use for manufacturing a drug for the  
treatment and prophylaxis of post-operative nausea and  
vomiting and for the control of nausea and vomiting  
25 induced by radiotherapy and cytotoxic chemotherapy.



**FIG 31**

26



~~Raman Intensity (A.U.)~~

~~FIG 4~~

27

~~Frequency (cm<sup>-1</sup>)~~

## ABSTRACT

New polymorphic forms of ondansetron, processes for  
5 preparing ~~them~~it, pharmaceutical compositions containing  
~~them~~it and ~~their~~its use as antiemetics

This invention relates to a new polymorphs of ( $\pm$ )1,2,3,9-  
10 tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-  
4H-carbazol-4-one, known under the INN of ondansetron, to  
a processes for preparing said polymorphs, to  
pharmaceutical compositions containing ~~them~~it and to  
~~their~~its use in the treatment and prophylaxis of nausea  
15 and vomiting. The invention provides a new stable  
polymorphic forms of ondansetron and a processes for  
manufacturing ~~them~~it at an industrial scale.